REMARKS

Claims 1-21 are pending in the application. Claims 17-21 have been withdrawn as directed to non-elected subject matter.

Claim 1 has been amended to correct grammatical errors. Claim 4 has been amended to correct the antecedent basis so that claims 5 and 6 properly depend therefrom. Claims 15 and 16 have been amended to correct any similarities between claim 12 and 15. Claim 15 is directed to a kit comprising a plurality of nucleic acid sequences and claim 16 has been amended to properly depend from claim 15. Support for the amendments is found throughout the specification, for example page 12, lines 23-32 through to page 13, lines 1-9. No new matter has been added by virtue of these amendments and their entry is respectfully requested.

Amendment and cancellation of the claims are not to be construed as an acquiescence to any of the rejections/objections set forth in the instant Office Action, and were done solely to expedite prosecution of the application. Applicants reserve the right to pursue the claims as originally filed, or substantially similar claims, in this or one or more continuation patent applications.

Restriction Requirement

Page 2 of the Office Action indicates that claims 17-21 have been withdrawn as directed to non-elected subject matter. Applicants hereby reserve the right to pursue the subject matter of the cancelled claims in one or more divisional patent applications.

Claim Objections

Claims 4, 12, 13, 15 and 16 are objected to. Applicants have amended the claims so that the claims recite a kit with at least one nucleic acid segments and a kit with a plurality of nucleic acid segments. The subject matter is, therefore, different and support is found , for example, page 12, lines 23-32 through to page 13, lines 1-9. Applicants respectfully request reconsideration and withdrawal of the objection.

Claim Rejections Under 35 U.S.C. § 112.

Claims 4-6 are rejected under 35 U.S.C. § 112, second paragraph, as failing to particularly point out and distinctly claim the subject matter which applicant regards as his invention..

Applicants have amended claim 4 to provide the proper antecedent basis. With the amendment, the antecedent basis is provided for claims 5 and 6.

In view thereof, applicants respectfully request reconsideration and withdrawal of the rejection.

Claim Rejections Under 35 U.S.C. § 102

Claims 1-12, 14, 15 have been rejected under 35 U.S.C. § 102 (e) as being anticipated by Wohlstadter *et al* (US 2004/00864233 A1). Applicants respectfully traverse.

Applicants' invention is directed in part to a circuit board biosensor apparatus wherein the apparatus comprises reference electrodes (see, for example, page 6, lines 25-30; page 7, lines 22-34; page 20, lines 22-33 through to page 21, lines 1-2; page 22, lines 21-34 through to page 24 lines 1-21; page 28, lines 7-33 through to page 29, lines 1-7; Examples 4.1 - 5.13); a plurality of nucleic acids attached thereto (see, for example, page 8, lines 13-29; page 10, lines 8-33; page 18, lines 19-33 through to page 20, lines 1- 15; page 21, lines 19-33 through to page 24, lines 1-26; page 26, lines 11- 32 through to page 27, lines 1-19; Examples 4.1-5.13); a means for measuring current (see, for example, page 7, lines 12-21; page 11, lines 1-15; page 18, lines 7-18; page 19, lines 29-33 through to page 20, lines 1-2; page 22, lines 9-20; page 27, lines 20-33 through to page 29, lines 1-7). The current is produced by the hybridized electrode bound nucleic acid segments and nucleic acid target sequences when an electric potential is applied.

Applicants also teach a pulse amperometric monitor for the electrochemical detection of nucleic acid sequences (Claims 4, 6 and dependent claims therefrom). See, for example, Figures

5, 6, 7-10, 12, and 15-18 showing data obtained with a pulse amperometric monitor and the text of the instant application on page 21, lines 2-33 through to page 22, lines 1-34. Also described is an amperometric monitor for the electrochemical detection of nucleic acid sequences that comprise pulse and intermittent pulse modes of operation. See for example, page 51, lines 1-33 through to page 56, lines 1-15; Figure 7 shows the nature of the varied modes of applying potential to the sensors.

In contrast to applicants' invention, Wohlstadter *et al.*, does not teach or disclose the use of an electrochemical apparatus for establishing an appropriate potential on an electrode surface so that an electrical current can be generated and used for nucleic acid detection. Moreover, in Wohlstadter *et al.* only optical signals are referenced and detection requires use of a photon detector. Wohlstadter et al., do not teach nor disclose electrochemical detection of target-dependent currents. Page 2, paragraph [0024]:

> ..adapted to apply a controlled voltage waveform effective to trigger electrochemiluminescence, photon detector means for detecting electrochemiluminescence form the sample and sample handling means.

Wohlstadter *et al.*, merely use a voltage waveform to trigger an electrochemiluminescence reaction which is measured in terms of emission of light. The emission of light is recorded via a visual means using a CCD camera (Wohlstadter *et al.*, page 6, paragraph [0110]). Detection of light emission, produced by electrically exciting labeled molecules, as opposed to measuring an electric current produced by hybridizing molecules, would inherently require significantly different supports, labels and methods. Wohlstadter *et al.*, do not teach nor disclose that a current is generated when a nucleic acid segment attached to the electrodes, hybridizes to a target nucleic acid sequence.

On page 4 of the Office Action, the Examiner alleges that Wohlstadter *et al.*, is inclusive of instant Claim 7:

> ECL assay methods are disclosed for detecting or measuring an analyte of interest, comprising (a) contacting one or more binding domains immobilized on an electrode, in which said contacting is

> with a sample comprising molecules leveled to an ECL label, (b) applying a voltage waveform effective to trigger ECL at said binding domains, which is viewed to be inclusive of instant claim 7, and (c) measuring or detecting ECL. (Pages 2, 6-7, 14). (Emphasis added).

Applicants respectfully disagree. Wohlstadter *et al.*, measures emission of light produced by applying a pre-determined voltage waveform. Consequently, supports, labels, and methods of applying a voltage waveform effective to trigger light emission (for an optical detection system) differ greatly from the application of specific electrical potentials effective to result in current generation when a target nucleic acid is captured at a surface, as in the instant invention.

The Examiner alleges on page 5, that:

> Further, in one embodiment, and simply by way of example, the signal processing means comprises a digital computer for transferring, recording, analyzing and/or displaying the results of each ECL assay. Which is viewed to be inclusive of instant claim 8.

Applicants respectfully disagree. As discussed above, applicants measure the current produced by the capture of a target nucleic acid. That is, the current is target induced and not applied by the apparatus. Moreover, the small, portable instrument that applies potential to a working electrode is the same instrument that transfers, records, analyzes and/or displays the current generated by the electrochemical assays as taught by applicants. (See for example, page 18, lines 7-18; page 19, lines 1-8; page 28, lines 7-30). Applicants apparatus is also tailored as a small, portable instrument that applies potential to a working electrode is the same instrument that transfers, records, analyzes and/or displays the current generated by the electrochemical assays. (See for example, page 19, lines 1-8).

On page 5, of the Office Action, the Examiner alleges that Wohlstadter *et al.*, is inclusive of instant Claim 5. Applicants respectfully disagree.

Applicants teach (Claim 5) a pulse amperometric monitor that simultaneously detects and quantifies levels of a plurality of targets on electrode arrays where dual sensors can be used as

elements of the array. The basic Electrode Design is described in section 3.2.1 of the application, with single and dual sensors shown in Figures 2A and 2B, respectively. The use of pulse amperometric monitors with dual sensors for detection of nucleic acid sequences is described on, for example, page 63, lines 7-33 through to page 65, lines 1-29.

Wohlstadter *et al.*, is directed to optical detection of an electrochemical reaction. Wohlstadter *et al.*, do not teach nor disclose an apparatus that detects and measures an electric current that is target-dependent and how to detect the generated current sequentially or simultaneously.

On page 6, of the Office Action, the Examiner alleges that Wohlstadter *et al.*, is inclusive of instant Claim 2:

> The formation of PMAMS on the surface of a composite electrode can be achieved by a variety of methods including photolithographic immobilization, microcontact printing and/or controlled application of drops of binding reagents to the surface through the use of microcapillary arrays or ink-jet printing.

Applicants respectfully disagree. Applicants invention teaches detection of current generated by the hybridization of a capture nucleic acid sequence on an electrode, and a target nucleic acid sequence. Therefore, the supports and electrodes generated by applicants are designed to detect electrically current generated by the hybridization. Wohlstadter *et al.*, do not teach or disclose how to design, make and use the electrodes of the instant invention which measure current and not light emission. The Examiner's allegations on page 6 and 7 are incorrect as Wohlstadter *et al.*, do not teach how to make and use electrodes that measure current generated by the hybridization reaction between the capture nucleic acid sequence and target sequence in an analyte. Undue experimentation by any disclosure of Wohlstadter *et al.*, would be required to identify the material needed to for the electrodes, the nucleic acid sequences, the attachment of the nucleic acid probes to the electrodes, the quantity of capture nucleic acids e.g. number per area (surface of electrode can be as small as 0.001 mm^2 to about 100 mm^2; page 8, lines 4-5), the pattern of nucleic acids on the electrodes, the length of nucleic acid capture

sequences, the solutions needed to measure the electric current, especially in view of detection of one nucleic acid sequence difference (see, for example, detection of single nucleotide polymorphisms on page 31, lines 8- 32 through to page 33, lines 1- 28) and the like.

In view thereof, Applicants respectfully request reconsideration and withdrawal of the rejection.

Claim Rejections - 35 U.S.C. § 103.

Claims 13 and 16 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Wohlstadter *et al.*, (Pub. No.: US 2004/00864233 A1) in view of Griffais *et al.* (EP 0407291A1). Applicants respectfully traverse.

Applicants have discussed in detail the invention and the differences between the instant invention and Wohlstadter *et al.* For the sake of brevity these arguments will not be presented again.

As noted above, Wohlstadter *et al.*, does not teach or disclose the generation of current produced by hybridizing molecules. In contrast, Wohlstadter *et al.*, electrically stimulate materials so that labeled compounds are excited and detected by the emitted light. The instant invention is directed to the detection of target-dependent electrical currents (not photons) generated by targets selectively captured on electrodes. Wohlstadter et al., teaches away from the instant invention as Wohlstadter *et al.*, fails to disclose means to generate and detect currents associated with captured nucleic acid targets.

Further, applicants teach specific types of captured nucleic acid targets that neither Wohlstadter *et al.* nor Griffais *et al.*, disclose either alone or in combination.

Applicants teach use of a 5'-phosphate modified reverse primer during a PCR step to generate double stranded PCR products that can subsequently be made into single stranded DNA by digestion with an exonuclease that acts on the 5'-phosphate modified strand. The forward

primer used in the PCR may be optionally modified as well, so that the single-stranded material remaining after exonuclease digestion is prepared for a) binding to the sensor surface and b) hybridization with a detector probe that has high selectivity for the nucleic acid target sequence of interest. (see, for example, page 14, lines 7-24; page 30, lines 3-33 through to page 31, lines 1-7).

In contrast to the instant invention, Griffais *et al.*, use an exonuclease to reduce the number of "false" PCR products generated in a PCR reaction. Griffais *et al.*, do not teach or disclose the use of an enzyme to modify a double-stranded PCR product and create a single-stranded DNA that is amenable to be captured on electrode surfaces and detected by means of a complementary detector probe that can be electrochemically detected. Accordingly, Wohlstadter *et al.*, in view of Griffais *et al.*, do not teach, suggest or make obvious the instant invention. Combining measurement of photon output (Wohlstadter *et al*) with a PCR reaction that is not designed with the generation of capture probes (Griffais *et al*) that can be attached to an electrode would not be obvious to one of ordinary skill in the art.

For at least the reasons given above, Applicants respectfully submit that Claims 13 and 16 and dependent claims therefrom are allowable over the cited references of record. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection.

CONCLUSION

Applicants respectfully request entry of the foregoing remarks and reconsideration and withdrawal of all rejections. It is respectfully submitted that this application with claims 1-16 define patentable subject matter and is in condition for allowance. Accordingly, Applicant respectfully requests allowance of these claims.

This response is accompanied by a petition for a three month retroactive extension of time and the required fee. The Commissioner for Patents and Trademarks is hereby authorized to charge the amount due for a three month retroactive extension of time and any deficiency in

any fees due with the filing of this paper or credit any overpayment in any fees paid on the filing, or during prosecution of this application to Deposit Account No. 50-0951.

Respectfully submitted,

AKERMAN SENTERFITT

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